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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/482,585	01/13/2000	David G. Hangauer JR.	19226/931 (R-5495)	7206

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EXAMINER	
PRASTHOFER, THOMAS W	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 11/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
file copy	09/482,585	HANGAUER ET AL.	
	Examiner	Art Unit	
	Thomas W Prasthofer	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *11,21 and 23-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

Status of the Application

Receipt is acknowledged of a response to a restriction/election requirement on 03 August 2001 (Paper No. 11).

Status of the Claims

Claims 1-69 are pending in the present application. Claims 11, 21 and 23-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Claims 1-10, 12-20 (in part) and 22 are pending and examined on their merits.

Response to Restriction and Election of Species with Traverse

Applicant's election with traverse of Group V(A), claims 1-20 (in part) and 22 in Paper No. 11 is acknowledged. Claim 11 recites that the second module comprises naphthalene (not indole, which is the elected invention). The traversal is on the ground(s) that all groups are closely related and would require common areas of search and consideration. This is not found persuasive because the examiner has provided reasons explaining why searching all groups presents a search burden and applicant has not indicated that any of the reasons are in error. Applicant submits that the inventions of Groups V and VI should be examined together as set forth in a prior oral restriction requirement. The examiner has provided reasons why searching these groups together would be burdensome. Applicant has not disputed the reasons provided in the restriction requirement mailed on March 28, 2001.

Applicant has suggested that the restriction requirement within groups IV-VII be replaced by an election of species (see groups A-I on page 4 of the restriction requirement). The different structures for the second module, or scaffold, have different chemical structures, different

classifications, and different chemical and physical properties. For example, the biphenyl scaffold is not planar as is naphthalene and the indole scaffold provides a hetero atom with different chemistry and geometry when compared to an aromatic carbon. Similarly, the claimed different specific molecular formulae for kinase inhibitors have different chemical, physical, and pharmacological properties as well as different classifications. Art anticipating or rendering obvious the use of one of these scaffold structures / specific inhibitor structures would not anticipate or render obvious the use of any of the other scaffold / inhibitor structures. Each invention would support separate patents. If, however, applicant submits evidence or identifies evidence now of record showing the different scaffolds and specific kinase inhibitors to be obvious variants, or clearly admits on the record that this is the case, the examiner will withdraw the restriction requirement and replace it with an election of species for search purposes. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims Rejections – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-7, 9-13, and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, it is not clear whether one or a plurality of combinations is being formed and selected by the claimed method because the claim recites first and second modules in the singular and combinations of modules in the plural. Clarification is requested.

B. In claim 1, the phrase "combining the first module with a second module" is not clear because the term "combine" does not specify a relationship between the two modules. By "combine," one can mean to place into the same container or structurally attach in some specific

or unspecified way. One of ordinary skill in the art would not be able to determine the metes and bounds of the claim because the means of combining modules is not clear. In the interest of compact prosecution, the examiner interprets "combine" to involve covalent attachment of the first and second modules.

C. In claim 1-7, 9-13, and 20, the term "module' does not provide a clear description of a structure or a group of structures that can be identified with certainty. One of ordinary skill in the art would not be able to determine what constitutes a "module." It is not clear if a "module" is a single molecular entity or if it can be a collection of functional groups or molecular fragments, for example. Clarification is requested. In the interest of compact prosecution, the examiner interprets a "module" to be a discrete, single molecule rather than a collection of separate functional groups.

D. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: (1.) method steps required for identifying functional groups and/or first modules that bind to protein kinase catalytic sites and (2.) method steps for assaying or in some way screening for protein kinase inhibition.

E. In claim 1, it is not clear if a "non-peptide scaffold" has no peptides bonds at all or if one or more peptides bonds are permissible so long as the scaffold is not a peptide. Clarification is requested. In the interest of compact prosecution, the examiner interprets "non-peptide scaffold" to include peptide bonds so long as a part of the molecule is not a peptide.

F. Claim 1 recites "a first module having one or more functional groups for binding to catalytic residues of the protein kinase." The claim language is not clear for the following reasons:

i) It is not clear whether the binding is covalent binding, non-covalent binding, or both. A "functional group" is defined in the art based upon a characteristic chemical behavior or reactivity. For example, a double bond between two carbons is a functional group and is defined based upon its chemical reactivity as opposed to its binding characteristics.

ii) It is not clear whether the recited functional groups actually do bind to catalytic residues of the protein kinase because the phrase "for binding to catalytic residues of the protein kinase" does not explicitly state that binding occurs.

iii) It is not clear if all of the functional groups on the module bind the catalytic residues of the protein kinase.

In the interest of compact prosecution, the examiner considers binding to be non-covalent binding and that all functional groups present are involved in binding to catalytic residues.

G. Claim 2 recites "attaching the first module to a peptide scaffold." It is not clear "attaching" involves the formation of a covalent bond or if "attaching" also includes ionic interactions and chelation, for example. In the interest of compact prosecution, the examiner interprets "attaching" to mean formation of a covalent bond.

H. In claim 2, it is not clear if the "one or more functional groups" identified as binding preferentially binding to the catalytic residues of the protein kinase are present on the first module, the peptide scaffold, or both. In the interest of compact prosecution, the examiner considers the "one or more functional groups" to be present on the first module only.

I. Claim 12 recites "wherein more than one first module is bound to the second module." The method steps of claim 1 do not provide for more than one first module. One would not know how the additional first module(s) relate to the second module (both structurally and functionally), at what point screening would take place (if at all) with respect to the additional first modules, or the order in which "combining" steps would take place.

J. Claim 18 recites "protein serine kinase." It is not clear if this term is equivalent to the art recognized term "serine-threonine kinase" or if there is a distinction between the two. In the interest of compact prosecution, the examiner considers "protein serine kinase" and "serine-threonine kinase" to be equivalent. Clarification is requested.

K. Claim 19 depends from claim 15, which recites tyrosine kinases, but lists three serine/threonine kinases. Clarification or correction is requested.

L. In claim 20, the term "specificity side chain elements" is not defined in the specification in such a way that one of ordinary skill in the art would know what types of structures are encompassed by the term. There is no art recognized definition for the term. Clarification of what structures are encompassed by the term is requested. It is also no clear what "adding" such elements to a combination of first and second modules means. "adding" could be interpreted as including the elements in a mixture without any covalent or non-covalent attachment to any of the modules. Clarification of what is meant by the term "adding" is requested.

Claims Rejections – 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-4, 7, 9, 12, 15, and 18 rejected under 35 U.S.C. 103(a) as being unpatentable over Sebti et al U.S. Patent No. 6,011,175 January 2000 and Hogan, Jr. U.S. Patent No. 5,705,585 January 1998.

Sebti et al. teach the production of a group of non-peptide CAAX mimetics that inhibit farnesyltransferase (abstract and summary of the invention, especially column 3). The inhibitors were synthesized to include amino and thiol functional groups which had been identified as binding to the catalytic site of the enzyme (column 1, lines 58-63 and column 2, lines 12-24). The portion of these molecules consisting of H_2N-CH(CA-NH-R)- CH_2-SH reads on the first module of present claim 1. When "A" is an oxygen atom, the molecular fragment also includes an amide and reads on present claim 3. The peptidomimetic labeled as "4" at the bottom of column 5 includes another, additional functional group (first module) consisting of a carboxylic acid that binds the active site of the target enzyme, which reads on present claims 3 and 12. The rest of the molecule (substituted biphenyl) reads on the second module (or scaffold) of present claims 1 and 9. A number of the described molecules were tested for the ability to inhibit the target enzyme, which reads on selecting combinations of first and second modules, which inhibit enzyme activity (in this instance farnesyltransferase, see table 3).

A molecular fragment containing the cysteine thiol and amino groups was attached to a peptide scaffold (Val-Ile-Met) which was later replaced by the non-peptide scaffold comprising biphenyl, which reads on the method steps of present claim 2 (column 3, line 44 – column 4, line 8). Consequently the molecular fragment corresponding the presently claimed "first module" reads on present claims 4 and 7.

In summary, the Sebti et al reference teaches the general method steps of identifying peptidomimetic enzyme inhibitors by a modular design that involves attaching one or more molecular fragments (corresponding to first modules) to non-peptide scaffolds (corresponding to second modules). The molecular fragments may comprise amide groups as well as other functional groups that are known to interact with the catalytic site of the target enzyme.

The Sebti et al reference does not teach a method for the identification of **protein kinase** inhibitors (or species thereof), the use of boronic acid, hydroxyl, vicinal tricarbonyl amide functional groups, or linear chains linking modules.

Hogan, Jr. teaches the design and synthesis of novel aminimide-based peptidomimetics including those that inhibit protein kinases (abstract and column 8, lines 31-40). Section 3 (summary) beginning in column 7 teaches a modular (building block) approach to the design peptidomimetic molecules (e.g. inhibitors of protein kinases). Column 7, lines 41-59 and column 8, lines 31-40 teach that the modules, or building blocks, contain appropriate atoms and functional groups that interact with binding sites of the native receptor (or enzyme). Molecular scaffolds are taught in column 7, lines 60-65. The synthesis of combinatorial libraries of peptidomimetics containing different combinations of modules is also taught (column 8, lines 44-49).

Column 10, lines 3-22 teach that the aminimide backbone is used as a scaffold (non-peptide scaffold second module) for the geometrically precise attachment of structural units (i.e. functional groups and/or modules containing functional groups). The reference goes on to state that "*specific molecular forms are chosen for screening and further study using several criteria.*" In other words, combinations of nonpeptide scaffolds attached to structural units (i.e. combinations of first and second modules) are selected for screening which, in turn, would lead to the selection of a peptidomimetic with the desired property such as the ability to inhibit an enzyme (protein kinase, for example). Column 42, lines 25-29 teaches that combinatorial libraries of peptidomimetics may be screened for interactions with enzymes using a variety of approaches known in the art.

Column 17, lines 46-56 teach that the aminimide backbone may comprise variants and mimetic of the purine ring or pyrimidines. Column 20, lines 11-13 specify groups including naphthyl groups that can be included with the scaffold. Column 18, lines 26-29 teaches that

functional groups such as carboxylic acids, amides, and lactones may be incorporated into the aminimide structure (i.e. first modules comprising these functional groups).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use peptide inhibitors and/or substrates of protein kinases as starting points for the design and testing of peptidomimetic inhibitors of protein kinase using the general method of Sebti et al. One would have been motivated to do so because the design of peptidomimetic inhibitors was well known in the art (see Hogan, column 4, lines 41-64) and kinases (both tyrosine and serine/threonine kinases) were well known regulators of a very large number of biological processes involved in disease, especially signal transduction. One would have had reasonable expectation for success because a number of peptidomimetic enzyme inhibitors had been synthesized at the time that the invention was made (e.g. by Sebti et al and Hogan).

3. Claims 1-9, 12-18, 20, and 22 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan, Jr. U.S. Patent No. 5,705,585 January 1998, Lawrence et al (1998) Pharmocol. Ther. 77(2):81-114, and Hirschmann et al. U.S. Patent No. 5,552,534 September 1996.

Hogan, Jr. teaches the design and synthesis of novel aminimide-based peptidomimetics including those that inhibit protein kinases (abstract and column 8, lines 31-40). Section 3 (summary) beginning in column 7 teaches a modular (building block) approach to the design peptidomimetic molecules (e.g. inhibitors of protein kinases). Column 7, lines 41-59 and column 8, lines 31-40 teach that the modules, or building blocks, contain appropriate atoms and functional groups that interact with binding sites of the native receptor (or enzyme). Molecular scaffolds are taught in column 7, lines 60-65. The synthesis of combinatorial libraries of peptidomimetics containing different combinations of modules is also taught (column 8, lines 44-49).

Column 10, lines 3-22 teach that the aminimide backbone is used as a scaffold (non-peptide scaffold second module) for the geometrically precise attachment of structural units (i.e. functional groups and/or modules containing functional groups). The reference goes on to state that "*specific molecular forms are chosen for screening and further study using several criteria.*" In other words, combinations of nonpeptide scaffolds attached to structural units (i.e. combinations of first and second modules) are selected for screening which, in turn, would lead

to the selection of a peptidomimetic with the desired property such as the ability to inhibit an enzyme (protein kinase, for example). Column 42, lines 25-29 teaches that combinatorial libraries of peptidomimetics may be screened for interactions with enzymes using a variety of approaches known in the art.

Column 17, lines 46-56 teach that the aminimide backbone may comprise variants and mimetic of the purine ring or pyrimidines. Column 20, lines 11-13 specify groups including naphthyl groups that can be included with the scaffold. Column 18, lines 26-29 teaches that functional groups such as carboxylic acids, amides, and lactones may be incorporated into the aminimide structure (i.e. first modules comprising these functional groups).

The Hogan Jr. reference does not explicitly teach the attachment of a first module to a peptide scaffold and replacing the peptide scaffold with a non-peptide scaffold, the use of boronic acid or vicinal tricarbonyl amide functional groups, scaffolds comprising indole for kinase inhibitors, inhibiting specified protein kinases, or protein kinase inhibitors that do not inhibit ATP binding.

Lawrence et al provide a summary of the state of the art in protein kinase inhibitors as of 1998. In the introduction, the authors write:

"*One might therefore expect that agents which are able to shut down catalytic activity of these oncogenic or overexpressed protein kinases should block uncontrolled cell growth... As a consequence, inhibitors of this family of enzymes ultimately may serve as new weapons in our arsenal for battling human disease and suffering.*"

In section 5.2, page 86, the authors write:

"*However, peptides do provide a structural foundation upon which peptidomimetics can be designed.*"

Page 100, in the right-hand column, teaches that a transition state analog can be used to generate a peptide-based inhibitor in which the phosphorylated tyrosine is replaced by either D- or L- 4-F tyrosine (phosphotyrosine analogs). One of the resulting inhibitors is competitive with respect to ATP and the other is not. The peptide portions of these inhibitors read on the presently claimed "specificity side chain elements" of claim 20. Page 101, left hand column, teaches a similar inhibitor comprising trifluorotyrosine and inhibitors in which the tyrosine hydroxyl is replaced by phosphino-, phosphonomethyl, and phosphono- groups. The

phosphonomethyl substitution of the tyrosine hydroxyl reads on a first module (phosphono functional group) linked through a one carbon chain (see present claim 13) to a phenyl scaffold (second module).

Page 104 of the Lawrence et al reference, right-hand column, teaches the design and testing of phosphotyrosine analogs that inhibit protein kinases Lck, Src, PLCγ-C, PI-3 kinase, Grb2, and SH PTP2-N (see presents claim 16 and 17 reciting $pp60^{c\text{-}src}$ and $p56^{lck}$, for example). The left –hand column of page 104 teaches four inhibitors of PI-3 kinase, each comprising a benzene scaffold with two attached modules. In each case, one attached module is an amide grouped linked to the scaffold through a methylene group. In the molecule labeled 139, a phosphono group (first module) is linked to the benzene scaffold through a one-carbon linker in which the carbon is substituted with an oxygen (see present claim 14).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the method steps of Hogan to make peptidomimetic protein kinase inhibitors. One would have been motivated to do so because Lawrence et al provide powerful motivation for the development of such inhibitors and suggest the development of peptidomimetics and tyrosine analogs specifically. Page 104, left column, middle of the page teaches a combinatorial approach to the design of PID-domain binding inhibitors. One would have had reasonable expectation for success because Hogan provides numerous examples of the successful use of his method to make peptidomimetics with a wide variety of binding/inhibiting activities.

With respect to the placement of first modules on peptide scaffolds and replacing the peptide scaffold with a non-peptide scaffold, this process is accomplished during the development of virtually all peptidomimetic molecules. One begins by testing a series of peptides for a desired activity in which a portion of each of the peptide or functional groups on the peptides are believed to interact with a target of interest (i.e. the catalytic site of a protein kinase). The portion(s) of the selected peptides that bind the catalytic site of an enzyme, for example, are placed onto non-peptide scaffolds to form peptidomimetics (see Hogan). In this sense, the synthesis of the peptide has attached the first module(s) to a peptide scaffold.

With respect to the use of any particular functional group such a boronic acid etc., such choices would have been well within the abilities of one of ordinary skill in the art as a matter of design choice.

Hirschmann et al. teach methods for the preparation of non-peptide peptidomimetics. Motivation for the preparation of such peptidomimetics, including enzyme inhibitors, is provided in column 2, lines 24-29. Column 4 teaches cyclic scaffolds with multiple variable R groups (first modules) attached. Column 6, lines 1-20 describes the general process of placing the chemical functionalities found in selected peptides onto non-peptide scaffolds in such a way that the spatial arrangement of the functionalities in the peptides are preserved. The process is exemplifies in column 6, lines 27-45. Selection of combinations of scaffolds and "modules" by a functional assay is illustrated in column 91.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the method of Hirschmann et al. to make peptidomimetic inhibitors of protein kinases. One would have been motivated to do so because Lawrence et al. provide motivation for making such inhibitors and Hirschmann et al. provide a means of producing such inhibitors for enzymes in general. One would have had reasonable expectation for success because the methods of Hirschmann and Hogan had both been successful in generating active peptidomimetics.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Thomas Prasthofer, Ph.D.

November 17, 2001